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Acute safety of beclomethasone dipropionate in a new CFC-free propellant system in asthmatic patients

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Hydrofluoroalkane-134a (HFA-134a) is a new chlorofluorocarbon (CFC)-free propellant for use in metered dose inhalers. It provides a more environmentally friendly alternative to CFC propellants because it does not contain chlorine which is responsible for ozone depletion by CFCs. Beclomethasone dipropionate (BDP) is widely used for inhalation asthma therapy and is most commonly delivered by a CFC propellant system. The present study evaluated the acute safety of BDP formulated with the new propellant (HFA-134a BDP) compared with BDP in a CFC-11/12 formulation by measuring the acute bronchial response in asthmatic patients.

The study was conducted as a randomized, single-blind, placebo-controlled, four-period cross-over trial. Asthmatic patients received eight inhalations of four treatment regimens (HFA-134a BDP, 1600 mg total dose; CFC-11/12 BDP, 2000 mg total dose; HFA-134a placebo and CFC-11/12 placebo) in random order over four study days. Forced expired volume in 1 s (FEV_1) was measured before and 2, 10, 20, 40 and 60 min after inhalation of the study treatments. The number of coughs was counted from the start of the first inhalation to 60 s after the last inhalation.

There were no statistically significant differences between the treatment groups for changes in FEV_1, for the number of coughs or for the occurrence or severity of bronchoconstriction.

In asthmatic patients withholding bronchodilators, the new HFA-134a BDP propellant system proved as safe and was as well tolerated as the current CFC-11/12 BDP system. The two propellant systems without active drug were also equally well tolerated.

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Introduction

Chlorofluorocarbons (CFCs) are used as propellants in metered dose inhalers (MDIs) which are the most frequently used delivery system for administration of drugs used in the treatment of asthma. The commonest CFCs in use are CFC 11 and 12. The important role that chlorine from CFCs plays in reducing the concentration of stratospheric ozone has been widely publicised (1). In response to the Montreal Protocol, which was established to reduce and eventually eradicate CFC production, an MDI containing beclomethasone dipropionate (BDP) reformulated using a CFC-free propellant, hydrofluoroalkane 134a (HFA-134a), has been developed.

Beclomethasone dipropionate is a synthetic halogenated corticosteroid which has been available since 1972 for use as an inhaled anti-inflammatory agent in the treatment of asthma. At present, it is most commonly delivered in a CFC propellant system; over 9 million are sold each year in the U.K. (Intercontinental Medical Statistics Limited). There are occasional reports in the literature of inhaled corticosteroids being associated with cough, wheezing and bronchoconstriction (2–6). Studies comparing the propellants HFA and CFC, without BDP present, show a very low frequency of these side-effects in normal healthy volunteers (7,8).

We undertook a study to evaluate the tolerability and acute safety of BDP formulated with the new propellant (HFA-134a BDP) compared with BDP in a CFC-11/12 formulation by measuring the acute bronchial response in patients with asthma withholding use of bronchodilators.

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Methods

STUDY PATIENTS

Adult patients with moderate asthma, who had been inhaling 400–1600 μg budesonide daily for at least the

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previous 6 months, took part in the study. Patients had stable, well-controlled asthma without exacerbations during the previous 3 months and each showed at least a 15% increase in forced expired volume in 1 s (FEV_1) within 15 min of inhalation of 200 μg of an inhaled β-agonist. Patients were taught satisfactory inhaler technique using a list of instructions from a patient information leaflet and were observed using their inhaler by a technician at each visit. Patients had to be capable of withholding their usual bronchodilator therapy for 6 h prior to each study day.

Patients were excluded if they were pregnant, had significant systemic or pulmonary disease other than asthma, had a recent respiratory tract infection, used β_1-antagonists, ACE inhibitors, theophylline, oral β_2-agonists, terbutaline (by subcutaneous infusion) or had used inhaled BDP during the previous 6 months. Patients who had a history of dependency on drugs or alcohol or who had smoked during the previous year were also excluded.

The study was approved by the Research and Ethics Sub-Committee, Birmingham Heartlands Hospital, and written informed consent was obtained from each patient who volunteered for the study.

SAMPLE SIZE

For this study, treatments were considered to be equivalent if the mean percentage change in FEV_1 after inhalation of the 'test' treatment (HFA-134a formulations) was no more than 15% different (twice the usual SD in FEV_1 measurements) from the 'reference' treatment (CFC-11/12 formulations). In a previous study, the estimate of the within-subject SD of percentage change in FEV_1 after inhalation of BDP was 6%. Based on this we calculated that 16 evaluable patients would provide three simultaneous 90% confidence intervals, each with a total width of less than 30%. The estimate of 6% was validated by a blinded interim analysis after 16 patients completed the study. The study had 95% power for concluding equivalence between the treatments with the within-subject SD of 6% and an equivalence definition of within 15%.

STUDY DESIGN

The study was of randomized, single-blind, placebo-controlled, four-period cross-over design, comparing lung function and symptom responses.

To optimize blinding (as in this study design the use of double dummies was precluded), dosing of study treatments took place in a separate room from the pulmonary function laboratory. Patients and the dosing supervisor were blinded only to which treatment was active or placebo because the HFA and CFC adapters were different in appearance. A second supervisor, blinded to all treatments, was responsible for the pulmonary function tests.

METHODS

Study days were separated by a minimum of 48 h. Study procedures started at the same time on each study day ($\pm$ 2 h). Patients withheld their bronchodilator therapy (inhaled salbutamol, terbutaline or oxitropium) for 6 h prior to each study day.

All eligible patients were randomly assigned a sequence of four treatment regimens, each contained in an MDI. Depending upon their sequence, patients received eight inhalations at 45 s intervals of each of the following treatments on study days 1, 2, 3 and 4, each dose being delivered under supervision:

1. 8 × 200 μg HFA-134a BDP (QVAR®, 3M Pharmaceuticals, Loughborough, UK; total dose 1600 μg);
2. 8 × 250 μg CFC-11/12 BDP (Allen and Hanburys, Greenford, UK; total dose 2000 μg);
3. 8 × HFA-134a placebo;
4. 8 × CFC-11/12 placebo.

Each active drug was given as eight inhalations of the highest strength inhaler available.

On study day 1, patients were required to rest for at least 15 min before a pre-dose FEV_1 measurement was performed. FEV_1 was measured using a dry bellows spirometer in accordance with the American Thoracic Society Guidelines (9). The best of three reproducible (within 100 ml) values were used in the analysis. FEV_1 measurements were taken at 2, 10, 20, 40 and 60 min post-inhalation. Following the final FEV_1 measurement, patients resumed their normal therapeutic regimen until the next study day. Pre-dose FEV_1 measurements on study days 2, 3 and 4 were required to be within $\pm$ 15% of the pre-dose FEV_1 measured on study day 1.

On each study day the number of times that any patient coughed was counted from the beginning of the first inhalation to 60 s after the eighth inhalation, the cumulative number of coughs being used for analysis.

Haematology, serum chemistry and urinalysis, a physical examination and a standard 12-lead electrocardiogram were performed at the pre-study day and at the end of the fourth study day. Adverse events were recorded throughout the study.

ANALYSIS

The primary safety parameter for this study was percentage change in FEV_1 from baseline up to 1 h after study drug administration on each study day. This was calculated as follows:

$$(FEV_1 \text{ pre-dose} - FEV_1 \text{ post-dose}) \times 100/(FEV_1 \text{ pre-dose})$$

A blinded analysis of FEV_1 data was performed when 16 patients had completed the study. This analysis was performed to ensure that the assumptions for the sample size calculation were met. The analysis was performed without breaking the blind and, therefore, no adjustment was made to the type 1 error.

The percentage change from pre-dose FEV_1 was compared between treatment groups using an analysis of variance (ANOVA) for a four-period cross-over design with sequence, subject within sequence, treatment and period as factors in the model.

Three treatment comparisons, involving active and placebo formulations of HFA-134a, were of interest:

1. HFA-134a BDP *vs.* CFC-11/12 BDP;
2. HFA-134a BDP *vs.* HFA-134a placebo;
3. HFA-134a placebo *vs.* CFC-11/12 placebo.

The null hypothesis was that the treatment mean percentage changes in FEV_1 were not equivalent (within ± 15%). Rejection of this hypothesis implies equivalence of the treatment means.

In each comparison, the first treatment listed is referred to as the 'test' treatment and the second as the 'reference' treatment. The 'test' mean was considered to be equivalent to the 'reference' mean if the 90% confidence interval (CI) for the difference between the two means was contained within an interval of ± 15%.

The null hypothesis of equal mean number of cough counts was tested using an ANOVA. Cough counts were a secondary safety parameter and were counted from the beginning of the first inhalation to 60 s after the eighth inhalation. Rejection of the null hypothesis implies a difference between treatments in mean cough counts.

Equivalence testing was done only for the percentage change in FEV_1; all other hypothesis tests were to test for differences between treatments.

Results

Of 18 patients enrolled into the study, a total of 16 patients (two men, 14 women) completed all four study days. Their mean (± SD) age was 50 (± 15) years. Two patients withdrew: one patient violated the protocol on entry to the study by taking >1600 mg budesonide and was withdrawn after completing study day 1; the second patient withdrew consent after completing study day 1 due to work commitments.

There were no statistically significant differences at the 5% level in the treatment sequence for any of the demographic characteristics evaluated (Table 1).

FEV_1 VALUES

There were no significant differences between the mean pre-dose FEV_1 values for the four treatment groups (P=0·825; Table 2) and no significant overall treatment effects with respect to the percentage change from pre-dose in FEV_1 at each of the post-dose assessments (P>0·05; Fig. 1). For each of the comparisons of interest, the 90% CI for the difference between the 'test' mean and 'reference' mean was well contained within the ± 15% interval. Therefore, the study treatments were equivalent with respect to the change from pre-dose FEV_1 for each of the three comparisons made (Table 2).

On eight occasions, five patients experienced falls in FEV_1 of ≥15% which were considered clinically significant by the investigator. There was no difference between the study treatments in the incidence of these falls (P=0·682; Table 3).

TABLE 1. Demographic characteristics

Characteristic	n=16
Gender	
Male n (%)	2 (13%)
Female n (%)	14 (88%)
Asthma duration	
1–5 yr n (%)	2 (13%)
>5 yr n (%)	14 (88%)
Age (years)	
Mean	50
Range	19–68
Height (cm)	
Mean	166
Range	149–183
Weight (kg)	
Mean	68
Range	41–89

COUGH COUNTS

Cough counts experienced by patients ranged from 0 (several patients on all study treatments) to 92 (one patient receiving CFC-11/12 BDP). The overall treatment effect was nearly significant, with a trend for the counts to be higher in patients receiving the CFC-11/12 treatments (P=0·061; Table 4). However, none of the pairwise treatment comparisons was significant.

OTHER OUTCOMES

Adverse events almost exclusively involved the respiratory system. Cough was reported by five patients, upper respiratory infection by two, a tight chest by one and bouts of sneezing by one (Table 5). There was no pattern to the adverse events reported and no evidence of them being more common in one treatment group than another. There were no significant abnormalities in the serum biochemistry or haematology.

Discussion

This study evaluated the acute safety of BDP formulated with a new CFC-free propellant, HFA-134a, by comparing it with a CFC-BDP formulation and HFA-134a placebo. In previous studies, the two propellants, HFA-134a and CFC-11/12, were investigated and had been shown to be equally safe in normal healthy volunteers (7,8). The present study compared the same propellants, both with and without the active drug, in patients with asthma, whose airways will be more sensitive to any irritant effects. Moreover, the patients recruited were regular budesonide users so had not previously been sensitized, or developed tolerance, to BDP.

The study design allowed direct comparison of the effects of both formulations on each individual patient by using a cross-over design. Any carry-over effects were thought to be

TABLE 2. Difference in percentage change from pre-dose FEV_1 at five time points post-dose

Comparison of interest (test *vs.* reference*)	Mean baseline FEV_1 litres (SD)	Difference in mean % change from pre-dose FEV_1 (SE) {90% CI†} [*P*-value‡]				
		Min post-dose				
		2	10	20	40	60
HFA-BDP *vs.* CFC-BDP	2·20	0·1	−1·2	−0·3	1·1	3·4
	(0·74)	(2·4)	(2·8)	(2·9)	(2·1)	(2·3)
	2·21	{−3·8, 4·1}	{−5·8, 3·4}	{−5·1, 4·4}	{−2·4, 4·6}	{−0·34, 7·2}
	(0·80)	[<0·001]	[<0·001]	[<0·001]	[<0·001]	[<0·001]
HFA-BDP *vs.* HFA-placebo	2·20	3·4	3·3	−0·2	1·2	3·2
	(0·74)	(2·4)	(2·8)	(2·9)	(2·1)	(2·3)
	2·21	{0·6, 7·3}	{1·3, 7·9}	{−5·0, 4·5}	{−2·3, 4·7}	{−0·54, 7·0}
	(0·82)	[<0·001]	[<0·001]	[<0·001]	[<0·001]	[<0·001]
HFA-placebo *vs.* CFC-placebo	2·21	−2·9	−3·7	2·3	−0·8	−0·04
	(0·82)	(2·4)	(2·8)	(2·9)	(2·1)	(2·4)
	2·24	{−6·9, 1·1}	{−8·3, 0·8}	{−2·5, 7·0}	{−4·3, 2·7}	{−4·0, 3·9}
	(0·81)	[<0·001]	[<0·001]	[<0·001]	[<0·001]	[<0·001]

*The reference mean is the mean of the second treatment listed in the comparison.
†90% CI for difference.
‡$P<0·001$ for all times and all comparisons. The *P*-value results from the test of the null hypothesis that the 'test' mean was more than 15% different from the 'reference' mean. Rejection at the 0·05 level implies acceptance of the alternative hypothesis that the two treatment groups are equivalent.

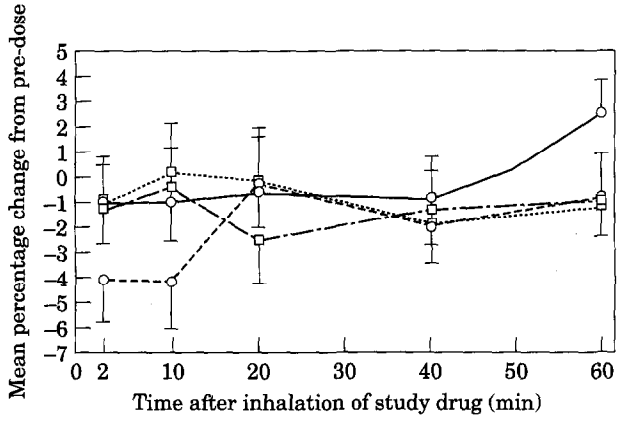

FIG. 1. Mean percentage change from pre-dose FEV_1 over time ($P>0·05$ at each time point). (—, HFA-134A BDP; – – –, HFA-134A placebo; - - - - -, CFC 11/12 BDP; – · – · –, CFC 11/12 placebo.)

negligible because patients received a single dose separated by at least 48 h of normal asthma therapy. Indeed, sequence effects were found not to be statistically significant. Patients received the highest daily dose of BDP a patient would be expected to take, representing 2000 μg CFC-11/12 BDP and 1600 μg of HFA-134a BDP. The highest strength of CFC-BDP for Becloforte is 250 μg, while the highest strength available for HFA-134a BDP was 200 μg. The inhalers were compared on a puff-for-puff basis, i.e. 8 × 250 μg for CFC-BDP and 8 × 200 μg for HFA-134a BDP.

The CFC and HFA inhalers used in this study were not identical in design owing to the physico-chemical properties of the HFA propellant on several aspects of the mechanical system (10). The HFA preparations did not contain a surfactant because HFA does not dissolve conventional surfactants (the BDP in the HFA inhaler is a solution of BDP). In contrast, the CFC preparations contained oleic acid as a surfactant. Furthermore, the valve on the HFA MDI did not contain a conventional neoprene diaphragm, which has been demonstrated to be adversely affected by the HFA propellant; the seal material was manufactured from a new elastomer which was compatible with HFA propellant.

We demonstrated no statistically significant differences between the propellants for changes in FEV_1 or the number of coughs. The CFC-free system was as safe and as well tolerated as the CFC system containing BDP or placebo in patients who required anti-inflammatory therapy and who were withholding bronchodilator medication.

The number of coughs was counted over a short period (from the beginning of the first inhalation to 1 min after the last inhalation) to try to distinguish between coughs directly related to inhalation of the treatments and those caused by other factors. On the whole, cough counts were low and, although there was a trend for them to be higher in the CFC-11/12 treatment periods, there was no statistically significant difference between the groups.

Paradoxical bronchoconstriction has been reported with various MDI products. A recent study (11) of 11,850 patients with asthma, to assess the frequency of paradoxical bronchoconstriction to CFC MDIs containing the

TABLE 3. Subjects with falls in FEV_1 of $\geq 15\%$

Subject identification number	Fall from pre-dose FEV_1 (time post-dose)			
	HFA-BDP ($n=16$)	CFC-BDP ($n=16$)	HFA-placebo ($n=16$)	CFC-placebo ($n=16$)
107		29·9% (2 min)	20·6% (2 min)	21·0% (20 min)
111		17·3% (10 min)		
112			17·2% (60 min)	
115	16·7% (10 min)			
116		15·0% (2 min)		21·3% (20 min)

TABLE 4. Cough counts for four study treatments

Cough counts	HFA-BDP ($n=16$)	CFC-BDP ($n=16$)	HFA-placebo ($n=16$)	CFC-placebo ($n=16$)	P-value*
Mean	5	8	4	8	0·061
Median	0	2	0	5	
SE	0·63	0·71	0·47	0·68	
Min–max	0–74	0–92	0–33	0–72	
Subjects with ≥ 1 cough (n)	7	10	7	9	

*The P-value is based on the overall test of treatment from ANOVA for a four-period cross-over.

TABLE 5. Adverse events affecting the respiratory system

Adverse event	Number of subjects (subject identification numbers)			
	HFA-BDP	CFC-BDP	HFA-placebo	CFC-placebo
Cough	4 (101, 102, 109, 116)	2 (109, 113)	2 (109, 113)	3 (102, 113, 116)
Tight chest	1 (205)	1 (205)	1 (205)	0
Sneezing	1 (109)	1 (109)	1 (109)	0
Upper respiratory tract infection	2 (106, 114)	0	0	1 (114)

surfactants oleic acid or lecithin and salmeterol xinafoate with lecithin, showed an overall incidence of 1·5%. Bronchoconstriction occurred within 5 min in these patients, and similar findings have been reported with BDP, where falls in FEV_1 of between 22 and 61% (2–5) have been shown. Shim and Williams previously suggested that the surfactant in BDP MDIs may be the source of coughing and wheezing (12). However, unlike CFC-based MDIs, HFA-BDP contains no added surfactant and is a solution, rather than a suspension, of BDP.

In the present study there were three decreases in FEV_1 observed at 2 min post-dose, which could have been a reaction to the study medication, propellants or excipients. There were five falls in FEV_1 occurring for the first time at a later time point after inhalation. These may have been caused either by patients withholding their bronchodilator therapy for the previous 6 h or, as has been previously reported, the repeated deep breath and forced expiration required for consecutive measurements of FEV_1 (13). All decreases in FEV_1 were not greater or more prevalent in any one of the treatment groups.

In asthmatic patients withholding bronchodilators, the new HFA-134a BDP propellant system proved as safe and was as well tolerated as the current CFC-11/12 BDP system. The two propellant systems without active drug were also equally well tolerated.

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